Effects Of Mouth Dissolving Mosapride Tablets (Mdmts) On Gut Recovery After Major Abdominal Gynecological Surgery (Mags)

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Abstract

Aim: To access whether receiving mouth dissolving mosaperide tablets (MDMTs) in immediate postoperative period in addition to routine care accelerates the recovery of upper and lower gastrointestinal function after major abdominal gynecological surgery (MAGS).

Patients & Methods: A randomized controlled study was conducted from December 2014 to December 2015. Patients scheduled to undergo abdominal hysterectomy were assigned to receive ***MDMTs*** beside routine care immediately postoperatively or routine care alone after surgery. patient's postoperative charts were reviewed to establish incidence of postoperative nausea, vomiting, use of analgesics, use of antiemetics, cases developing postoperative ileus (POI) (nausea, vomiting, distention, absence of bowel sounds) and its degree mild (resolved spontaneously on basic support), moderate (required nasogastric tube insertion beside basic support), severe (POI that resist management lines including antiemetic and persist for > 2 days), time to discharge and time from end of surgery to first postoperative hearing intestinal sounds, toleration of fluids intake, toleration to solid foods intake, passage of flatus, as well as first defecation.

Results: A total of 120 patients were randomly assigned to receive ***MDMTs*** (n=60, 2 were excluded, 58 were available for intension to treat analysis) or routine postoperative care alone (n =60, 4 were excluded, 56 were available for intension to treat analysis). The mean time to first hunger, toleration of liquids and solids, bowel movement, flatus as well as first defecation were significantly shorter in participants whom assigned to receive ***MDMTs*** ($P = 0002$, $P = 0.027$, $P < 0.0001$, $P = 0.0001$, $P < 0.000$, $P = 0.0006$ respectively). Participants assigned to receiving MDMTs than routine care experienced significant postoperative nausea ($P = 0.004$) vomiting ($P = 0.005$) and mild and moderate POI ($P = 0.008$, $P = 0.02$ respectively). ***MDMTs*** intake was well tolerated and well accepted by patients and no intervention – related side effects were observed.

Conclusion: Receiving ***MDMTs*** after MAGS accelerates the time of gut recovery, shortened the length of hospital stay as well as reduce the incidence of POI. This simple, inexpensive and well tolerated treatment could be added to routine postoperative care of major gynecological abdominal surgery patients.

Keywords: Postoperative ileus, major abdominal gynecological surgery, mouth dissolving mosapride tablets, mosapride citrate, abdominal Hysterectomy.

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Introduction

Postoperative ileus (POI) that develops after elective abdominal surgery is a transient state of abnormal bowel motility from the time of surgery until the return of normal gastrointestinal function[1]. POI contributes to patients discomfort, causes nausea, vomiting, abdominal distension, electrolyte imbalance, dehydration, prolonged hospitalization, sepsis,

hospital aquried infection, deep-vein thrombosis and pulmonary aspiration. This results in increase hospital costs and the thirty day readmission rate[2]. POI has been more specifically defined as at least two episodes of emesis of at least 100ml each within 24 – hour period, with associated abdominal distention and absent bowel sounds[3], according to this definition, up to 14% of patients after laparotomy for gynecologic surgery affected by severe POI[4]. POI increase length of hospital stay (LOS), after abdominal hysterectomy by a average of 3.7 days[5]. Furthermore POI was classified based on symptoms severity, intervention needed to rectify patient's condition into mild, moderate, severe POI[7], thus high variation in POI incidence reporting[1,4].

Despite the high incidence of ileus, preventive therapeutic options remain limited. Several efforts that include early resumption of feeding[6], gum chewing[7], coffee consumption[8,9], adequate pain control[10,11] and administration of prokinetic compounds (such as serotonin receptor againsts[12,13], neostigmine[14], alvimopam[15] and ghrelin agonists[16], have been made to prevent ileus. Unfortunately, none of these strategies has been completely successful[11].

Mosapride citrate is a selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist that is found to be effective on the upper gastrointestinal tract (UGIT)[12] as well as lower gastrointestinal tract (LGIT) including rectum and anus[17-22]. Researchers found that mosapride reduces the duration of POI after colectomy[12,13]. Recently, mosapride is available as mouth dissolving tablets (MDTs), that is fast dissolving in mouth without need of water and at very lower risk of choking during oral intake as well as increased bioavailability (rapid absorption) due to pregastric absorption[23]. Thus in this trail it was hypothesized that, adding mosapride as MDTs immediate after major abdominal gynecological surgery (MAGS) to routine postoperative care may reduce nausea, vomiting, so may increase amount of food intake and shorten the time to the apperrance of first flatus and defecation through acceleration the motility of UGIT and LGIT via stimulation of the 5HT4 receptor.

The aim of the present study was to evaluate whether mouth dissolving mosapride tablets ***(MDMTs)*** shortened the duration of POI after MAGS.

Patients and Methods

This randomized study was conducted at Benha University Hospital, Obstetrics and Gynecology Department, Benha, Egypt, from December 2014 to December 2015. Ethical approval was obtained from Benha Faculty of Medicine Ethics committee. Women were asked to participate if they were scheduled to undergo laparotomy for benign, premalignant, early malignant gynecologic condition. Women were excluded if they had an active intraabdominal malignancy, bowel perforation, pre-existing bowel disease, a history of abdominal or pelvic irradiation, any known hypersensitivity or allergy to mosapride citrate, compromised liver function, clinically significant cardiac arrhythmia, chronic constipation (defined as ≤ 2 bowel movements per week), a need for intensive care for > 24 hours postoperatively, a need for nasogastric tube drainage or a bowel anastomosis. Patients were also excluded if they were deemed unsafe for administration of ***MDMTs.***

The study details were explained to all enrolled women. All participants gave written informed consent before inclusion in the trial. Randomization was performed when women were admitted to gynecologic department. Eligible women were assigned randomly to 1 of 2 group ,where consecutively numbered, opaque, sealed envelopes were opened sequentially. Envelope randomization was performed with the use of computer – generated code running a blocked randomization protocol. Group A served as the control group and received only routine postoperative care i.e. no active treatment, group B (the ***MDMTs*** group) intake 3 tablets of mouth dissolving mosapride citrate 5mg (FLUXOPRIDE(R), Marcyrl Pharmaceutical Industries. Elobour city– Egypt) every 8 hours beginning immediate postoperatively as soon as the patient could do, under supervision of a nurse or resident, and continued up to first defecation or maximal 7 days. Patients and providers were not masked to group assignment, but individuals reviewing charts were. After enrollment, the same usual clinical protocol was implemented, women were underwent either general endothracheal anesthesia (GETA) alone or GETA with epidural analgesia or spinal anesthesia with sedation. All women in this trail were underwent abdominal hysterectomy, in most were total with bilateral salpingectomy(BS) for women under age of fifty or with bilateral salpingo-oophorectomy (BSO) for women with age > 50 year. Operations were done by residents, specialists, consultants.

Our hospital postoperative care protocol featured, early ampulation (as soon as possible as patients can), early feeding, (liquid diet was begun and progressed to solid diet as soon as patients can tolerate), prophylaxis for stress induced gastritis in form of histamine H2 blockers for 24 hours after surgery, adequate intravenously fluid, intravenous antibiotics and analgesics, which usually were parentral non steroidal anti-inflammatory

drugs (NSAIDs) but may be opioid (Nalbuphine 20mg dilutated in 20 ml saline given as 5ml as patients needed). The use of a preoperative bowel preparation and the advancement of diet postoperatively were at discretion of the surgeon overseeing the patient.

For nausea and vomiting in participants in this trail, prokintic durgs as metclopramide was avoided, while centrally activity agents were used as, cyclizine (Emetrex-Amonn pharmaceutical Co. S.A.E, El-Obour City, Cairo, Egypt) 50mg / 1ml IV or IM was firstly trided, after which (ondansetron) 8 mg IM or IV (Danset 8 mg ample, ADWIA Co. S.A.E., 10th of Ramadan City. Egypt) may be used.

The defined primary outcome measure was the time to the first passage of flatus after surgery. The secondary outcomes were the time to first defecation, time to toleration of a solid food, time to first bowel movement, any potential side –effects of postoperative MDMTs intake, nausea, incidence of vomiting, whether antiemetics were needed, analgesic requirements, incidence of POI and its type, rate and Length of Hospital Stay (LOS).

The time to the first bowel movement was defined as the time to the first audible bowel sound during routine postoperative care. The time to tolerance of solid food was measured from end of surgery (defined as when the patients fully woke up from anesthesia) until the patient tolerated the intake of solid food (any food that required chewing) without vomiting or experiencing significant nausea within 4 hours postprondial. Postoperative gut recovery was considered only after passage of first flatus with absent both abdominal distension and vomiting. POI were categorized a mild if symptoms resolved spontaneously on basic support, moderate if vomiting persisted and nasogastric tube insertion was needed, severe if symptoms persisted for > 2 day and resisted the routine treatment[7]. The symptoms and signs of ileus were evaluated 4 time daily including checking bowel sounds by a doctor who was blinded to the study allocation. Patients were instructed to record and notify, doctors whom evaluate them the time of first occurrence of flatus and defecation as well as time of first hunger, toleration of liquids and toleration of solid food.

Unfortunately, complete blinding after the assignment of the intervention could not be achieved because the unavailability of placebo identical to fluxopride in Egypt easily (the drug that used in the treatment interventional group). The hospital discharge criteria were stable vital signs, with no fever (defined as body temperature $\geq 38.5°C$) for at least 24 hours, the ability to ambulate without assistance, normal urination and defecation, the ability to tolerate solid diet without vomiting and the absence of any complications after surgery.

As all the studies, to date of beginning of this trail, that evaluate the mosapride role in POI had included only patients who had undergone colonic surgery[12,13]. Thus a non blinded pliot trail of 20 patients in each group (I and II) before the present trail was done. The mean time to flatus was 45.4 ± 14.4 hours in group I and 36.6 ± 12.6 hours in group II. Based on these data, minimum of 50 patients were needed in each group at study power of 90%, and a significance level of 0.05. The decision was made to enroll 120 women in this trial to account for a dropout of 20% (SISA)[24].

Statistical analysis was performed by Medcalc easy – to – use statistical software for windows desktop (www.medcalc.org) 2016 (Medcalc, software, bvha) (25). Continuous variable were presented as mean ± standard deviation (range) and between group differences were compared using independent samples (unpaired) student's t test. Categorical variables were presented as number (percentage) and compared using chi-square test. Risk ratios (relative risk) were estimated with the use of COX's proportional Hazad modeling. An intention to treat protocol was used. A $P < 0.05$ was considered statistically significant.

Results

Of the 120 patients who consented, 60 patients assigned randomly to the MDMTs group and 60 were assigned to control group. Six patients (2 in MDMTs group and 4 in control group) were excluded after randomization because they no longer fulfilled the inclusion criteria (Fig. 1).

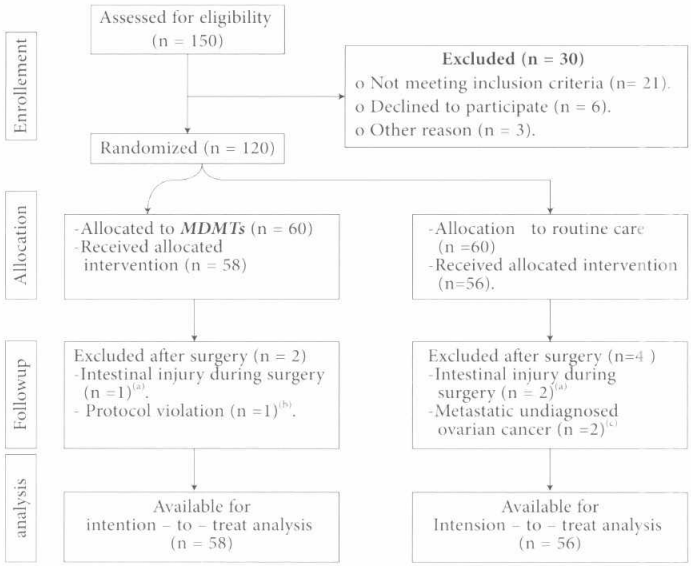
Table 1, shows the comparison of basic demographic and clinical criteria between patients who received MDMTs beside routine care and patients who received routine care only (control group), the two groups patients were matched at baseline without no differences in age, body mass index, ASA physical status, previous pelvi - abdominal surgery or comorbidites. The indications for hysterectomy were perimenopasual bleeding with failure of medical treatment (64.9%), precancerous conditions (27.1%), fibroids uteri (24.5) and adenomyosis (13.1%).

Table 2 shows that, there were no difference between both groups, regards types of abdominal incision, primary surgery, type of anesthesia, operative time, operative blood loss, the primary surgeon experience and intraoperative complications.

Table 3, shows the efficacy outcomes, the mean postoperative time to, first hunger, toleration of clear liquids, toleration of solid diet, first bowel movement, first flatus, and first defecation were significantly shorter in treatment group with ***MDMTs*** than in control group of routine postoperative care, p value were 0.002, 0.027, < 0.0001, 0.0001, <0.0001,<0.0006 respectively. In addition, the incidence of postoperative nausea and emesis were more in control group than treatment group, p value were 0.004, 0.007, respectively. The need for postoperative antiemetics were more in control group than MDMTs group (P = 0.007). Also, the LOS was significantly shorter in MDMTs group than control (P = 0.007). As regards patients whom developed POI there were no clinical or radiological signs of mechanical obstruction or abnormal laboratory results that support periotonitis so, conservative therapy, which primarily consisted of observation and basic support, was successful. Mild symptoms were seen in 17 patients (30.3%) in control group in comparison to 6 patients (10.3%) in ***MDMTs***. All patients were treated by stop oral feeding, ***MDMTs*** was not stoped, Intravenous fluid administration and antiemetic intravenously as previously described. Two patients in MDMTs group and 9 patients in control group developed moderate POI and they required insertion of nasogastric tubes for gastric decompression. Also the two patients whom developed moderate POI in treatment group, ***MDMTs*** continued to be used without stoping. In three patients in control group, POI were classified severe as symptoms were persisted more than 2 days and were resisted to the usual lines of managements. Three patients in this trail, needed reoperation due to inadequate hemostosis during primary procedures, while three patients in ***MDMTs*** group and four in control group were readmitted due to wound infection, need for secondary suture and evaluation for healing of urinary bladder injuries during the primary procedures (one in treatment group and 2 in control group, this three patients were discharged with urinary catheter and readmitted 2 weeks later for re-evaluation and found the bladder injuries were healed). Four patients needed intraoperative blood transfusion during primary procedures and three during reoperation.

Table 4 shows, analysis of patients demographic and clinical characteristics, according to presence or absence of postoperative ileus, patients who received MDMTs after surgery were less likely to have POI (21.6% Vs 64.9%; P < 0.0001). Furthermore, receiving MDMTs after surgery was an independently protecting intervention against the development of POI as shown in table 5.

Fig.(1): CONSORT flow chart of participants in mouth dissolving mosapride tablets



Abbreviations: **CONSORT:** Consolidated standards of reporting trials, MDMTs: Mouth dissolving mosapride tablets, the intension to treat (ITT) population was defined as all patients who were randomized to and used the investigational durg at least once.

(a): intestinal injuries were happened intraoperatively.

(b): one patient forget to intake the MDMTs in the first postoperative day.

(c): Two patients after laparatomy found to had metastatic ovarian tumos.

Table (1): Baseline demographics and clinical criteria of patients in MDMTs group after MAGS compared to control group.

Variable	MDMTs group (no = 58)	Control group (no = 56)	P value
Age(*) (years)	49.5 ± 6.7 (43.6-65.8)	48.6 ± 7.1 (42.6 – 66.8)	0.48
BMI(*) (kg/m²)	30.6±5.6 (25.6 – 38.8)	29.9 ± 6.1 (26.7 -39.5)	0.52
Parity(*)	3.1 ± 1.2 (0-8)	3.2 ±0.9 (0 – 9)	0.61
Prior pelvic-abdominal surgery(**)			
- None	38 (65.5)	36 (64.2)	0.88
- CS	15 (25.9)	16 (28.6)	0.74
- Others	5 (8.6)	4 (7.2)	0.70
Indication for hysterectomy(**)			
- PMB	28(48.3)	25 (44.7)	0.70
- Precancerous condition	9 (15.6)	9 (16.0)	0.95
- Fibroids	13(22.4)	15 (26.8)	0.58
- Adenomyosis	8(13.7)	7 (12.5)	0.85
Comorbidities (**)			
1- None.	35(60.4)	31 (55.6)	0.60
2- HTN	10(17.2)	9 (16)	0.86
3- DM	4(6.9)	6 (10.7)	0.47
4- CVD	3(5.2)	4 (7.1)	0.67
5- Others	6(10.3)	6 (10.7)	0.94
ASA(**)			
I	31(53.4)	26 (46.4)	0.45
II	27(46.6)	30 (53.6)	0.45
III	0	0	0

Abbreviation:* MDMTs:** *Mouth dissolving mosapride tablets,* ***MAGS*:Major abdominal gynecological surgery,* ***BMI****: Body mass index,* ***CS*** *: Cesarean section,* ***HTN****: Hypertension,* ***DM****: Diabetes mellitus,* ***CVD****: Cardiovascular diseases,* ***ASA****: American society of anesthesiologists physical status,* ***PMB****: Perimenopausal bleeding.*

- Values were given as mean ± standard deviation (range) or number (percentage)***

- P < 0.05 : statistically significant.

Table (2): Intraoperative variables of patients in ***MDMTs*** group after MAGS compared to control group.

Variable	MDMTs group (no = 58)	Control group (no = 56)	P value
Incision type**			
- Vertical midline.	11 (18.9)	10 (17.8)	0.88
- Pfannestiel	47(81.1)	46 (82.2)	0.88
Primary surgery**			
- TAH with BSO	13(22.4)	14 (25)	0.74
- TAH with BS	34(58.6)	31 (55.4)	0.73
- SAH with BS	8(13.7)	7 (12.5)	0.85
- SAH with BSO	3 (5.2)	4 (7.1)	0.67
Anesthesia**			
- GETA alone	35 (60.3)	30(53.6)	0.47
- GETA with epidural	6 (10.3)	11 (19.6)	0.16
- Spinal with sedation	17 (29.3)	15 (26.8)	0.76
Operative time, min*	80 ± 30 (60 -150)	85 ± 35 (65 – 160)	0.71
Operative blood loss, ml*	550±120 (250-2300)	5.25±140 (250 – 2100)	0.30
Intraoperative complications**	3 (5.2)[(a)]	4 (7.2)[(a)]	0.65
Intravenous fluids (min)*	34.50 ± 980 (1500-4500)	36.50± 9.50 (1500 – 5000)	0.27
Primary surgeon experience**			
- Trainee (≤ 7 year)	43 (74.2)	40 (71.4)	0.73
- Consultant (> 7 year)	15 (25.8)	16 (28.6)	0.73

Abbreviation:* MDMTs:** *Mouth dissolving mosapride tablets,* ***MAGS*: Major abdominal gynecological surgery,* ***TAH:*** *Total abdominal hysterectomy,* ***SAH****:Subtotal abdominal hysterectomy,* ***BS:*** *Bilateral salpinogectomy, BSO: Bilateral salpingo-oophorectomy,* ***GETA****: General endotracheal anesthesia.*

- Values were given as mean ± standard deviation (range) or number (percentage)***

- P < 0.05 : *statistically significant.*

[(a)]Three patients, one in MDMTs and two in control were with bladder injury, while 4 patients, 2 in each group were required blood transfusion.

Table (3): Outcome variables of patients in MDMTs after MAGS compared to control group.

Variable	MDMTs group (no = 58)	Control group (no = 56)	P value
Postoperative time to* :			
- First hunger (h)*	18.2±12.7(14-36)	25.3±13.8 (18-40)	0.002
- Toleration of clear liquids, (h)*	15.2±8.4(10-30)	18.8±8.8(12-38)	0.027
- Toleration of solid diet (h)*	35.1±11.2(28-52)	51.5±17.7(38-62)	0.0001
- First bowel movement, (h)*	34.8±8.9(26-52)	42.6±10.9(28-58)	0.0001
- First flatus, (h)*	36.8±9.8(26-54)	45.6±10.7(38-66)	0.0001
- First defecation (h)*	44.9±12.8(36-64)	52.8±10.9(46-74)	0.0006
Postoperative nausea**	14 (24.1)	28(50.0)	0.004
Postoperative emesis**	10(17.2)	23(41.0)	0.005
Postoperative ileus symptoms**			
- Mild	6(103)	17(30.3)	0.008
- Moderate	2(3.5)	9(16.0)	0.02
- Severe	-	3(5.3)	0.07
Postoperative hospital stay,(h)*	52.3±24.5(40-72)	68.7±38.7(48-90)	0.007
Use of postoperative antiemetics**	13(22.4)	26(46.4)	0.007
Postoperative analgesia*			
-Total narcotic dose (Nalbuphire), mg.	25.9±9.2 (20-40)	28.5± 9.8(20-40)	0.126
-Total parental NSAIDs (diclofenec sodium mg)	165.6±39.5(75-300)	125.4 ± 38.5 (75 – 300)	0.174
Readmission**	3(5.2)[a]	4.(7.1)[a]	0.67
Repeat surgery**	1 (1.7)[b]	2(3.4)[b]	0.56

Abbreviation: MDMTs: *Mouth dissolving mosapride tablets,* ***MAGS:*** *Major abdominal gynecological surgery,*
- Values were given as mean ± standard deviation (range) or number (percentage)***
- P < 0.05 *: statistically significant.*
[a]: Seven readmission, due to wound infection, need for secondary suture, bladder injures reevaluation.
[b]: Repeated surgery due to inadequate hemostasis during primary procedures.

Table (4): Patients demographic and clinical criteria according to presence or absence of postoperative ileus symptoms in MDMTs trail.

Variable	Patients with POI (no = 37)	Patients without POI (no = 77)	P value
Age > 55 years	11 (29.7)	29 (37.3)	0.42
BMI > 30 kg/m²	15 (40.5)	21 (27.2)	0.15
Prior pelvi – abdominal surgery	15(40.5)	25(32.4)	0.39
Trainee (≤ 7 years)	32 (86.4)	51 (66.2)	0.23
Consultant (≥ 7 years)	16(43.2)	15 (10.4)	0.007
TAH	27 (72.9)	65 (84.4)	0.14
SAH	5 (13.5)	17 (22)	0.27
MDMTs intake	8(21.6)	50 (64.9)	< 0.0001

Abbreviation: MDMTs*: Mouth dissolving mosapride tablets,* ***MAGS****: Major abdominal gynecological surgery,* ***TAH:*** *Total abdominal hysterectomy,* ***SAH:*** *Subtotal abdominal hysterectomy,* ***POI:*** *Postoperative ileus,* ***BMI*** *: Body mass index.*
- P < 0.005 : statistically significant.

Table (5): Univariate and multivariate analysis for risk factors for postoperative ileus after MAGS.

Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	P value	RR	95% CI	P value
Age (<55 (vs) > 55 year)	1.5	0.6-3.4	0.32	1.3	0.5-3.2	0.48
BMI (< 30(vs) > 30 kg/m2)	1.4	0.7-2.6	0.39	1.3	0.7-2.8	0.41
Prior pelvi - abdominal surgery	1.5	0.7-3.2	0.29	1.3	0.6-1.4	0.49
Trainee (≤ 7 year)	2.3	0.9-5.4	0.08	1.8	0.7-4.9	0.15
Consultant(>7year)	2.5	1.3-5.1	0.007	1.8	0.8-3.9	0.13
MDMTs intake	0.2	0.1-0.5	0.0002	0.2	0.1-3.9	0.001
TAH	2.5	1.4-5.6	0.14	1.9	0.1-0.6	0.34
SAH	1.2	0.7-2.6	0.34	1.8	0.8-3.9	0.13

***Abbreviation: MDMTs**: Mouth dissolving mosapride tablets, **MAGS:** Major abdominal gynecological surgery, **POI:** Postoperative ileus, **RR** : releative risk, **95% CI:** 95% confidence interval, **TAH:** Total abdominal hysterectomy, **SAH:** Subtotal abdominal hysterectomym, **BMI**: Body mass index*
*- **P < 0.05** : statistically significant.*

Discussion

The current randomized trial showed that receiving MDMTs after MAGS for benign and precancerous gynecological conditions improved both gastric and intestinal recovery as, receiving MDMTs shortened the time to first bowel motility and the ability to tolerate food as well as decrease the incidence of postoperative nausea and vomiting. Moreover, a regression model showed that receiving MDMTs during the early postoperative period was independently protective against the development of POI. Thus shorting the postoperative length of the hospital stay so results in overall cost saving. The MDMTs is, simple, well tolerated, easy to use monthly rapidly dissolving tablets, does not need water to receive it as usual oral tablets, Fruits flavour so improve month status and available as well as has low cost if compared to other pharmacologic agents for POI management as opioid receptor antagonists and ghrelin receptor agonists.

Despite that, POI is usually self-limited, it is an inevitable sequale of any intraperitoneal surgery and cloud increase the cost of major abdominal surgery. The POI is multifactorial and poorly defined pathophysiologic condition. There are many contributory factors to POI including the effect of surgical manipulation, the induction of an inflammatory response, the giving the opioids, the disturbances in gastrointestinal hormone activity and electrolytes fluctuations as well as the autonomic dysfunction[16]. Moreover, the therapeutic options for POI prevention still limited.

On reviewing English- language literature only 2 trials found to evaluate role of mosapride citrate in reducing POI[12,13]. **Narita et al.** randomly assigned 40 patients to receive either 15 mg mosparide usual mouth tablets with 50 ml water three time a day, starting on postoperative day 1 or 50ml water on the same schedule after hand assisted laparoscopic colectomy for carcinoma. The patients whom received mosapride experienced significantly shorter first bowel movement (defecation) (48,5 Vs 69.3 hours, p = 0.014), found to have shorter time for gastric emptying (proved by [^{13}C]. acetate breathes) (27.9 Vs 35.3 min, P = 0.029). Postoperative LOS was also significantly shorter (6.7 Vs 8.4 days, P = 0.039). Also, the time for first flatus was found to be shorter in mosapride arm but the difference was not statistically significant (32.7 Vs 39.1, p = 0.27). Likewise Toyomasn, et al. accessed role of mosapride in thirty patients with colon cancer whom underwent colectomy and they divided them into mosapride group, received 15mg mosapride tablets orally with minimal water amount three times a day, starting on postoperative day 1, and control group, received only a minimal amount of water in the same schedule. They found that the time to first flatus and defecation were significantly shorter in the mosapride group. Also they found that amount of food intake was larger in mosapride group and the motility index was higher in antrum and duodenum in mosapride group.

In the present study, POI symptoms were more common in the routine care group than in the MDMTs group. Furthermore, the need for antiemetics was significantly

lower in MDMTs group this may be attributable to reductions in bloating and distension that caused by increase gastric emptying as well as by accelerated passage of the first flatus. In addition, patients who receive MDMTs were tolerate clear fluid, solid food earlier as well as they were discharged also earlier than patients in the control group.

The results of this study may be very useful as a reference when major abdominal gynecological surgery is considered, repeated prior pelvi – abdominal surgery resulted in adhesion, and in those patients when hysterectomy is later needed, a degree of adhesolysis is used commonly and this found to increases the risk for POI during MAGS.

Mosapride is a prokinetic drug of a proved value in chronic gastritis its usual dose is 15 mg, three times a day. Mosapride has no effect on the dopamine D2 receptor or other receptors besides the 5-HT4 receptor, and so no severe adverse effect have been observed[27]. Animal studies proved its prokinetic effect on UGIT and LGIT postoperatively so reducing POI, as mosapride is highly selective for 5-HT4 receptor which were present in the large intestine as well as stomach[17]. So we chose mosapride because it is safe and inexpensive. Also, we chose this formula of drug as be easy to use, does not need water for intake and improve mouth health as well. We observed no significant adverse effects with MDMTs in immediate postoperative period after MAGS, confirming the relative safety of the usual dose of mosapride as well as the used drug formula.

This study had several strengths, which include the fact that it was a prospective randomized investigation and the two groups were matched regarding baseline demographic, clinical and surgical profiles. Moreover, the fact that the investigation was performed at a single institution by a comparable team of surgeons probably increases the validity of our results. On the contrary, this study limitation were, the study was conducted in a single –blind, not a double – blind manner as we did not have a placebo group thus we don't know whether there were any placebo effects and the patients were not blinded; this may have affected the effect of mosapride to small extent. Further double blinded placebo controlled trail may be necessary to confirm the results of this trail.

Conclusion

The data of this study, despite its limitations, suggest that receiving mouth dissolving mosapride tablets significantly improve gastrointestinal recovery without adverse effects, and significantly reduce postoperative ileus as well as postoperative length of hospital stay after major gynecological abdominal surgery for benign and precancerous gynecological conditions.

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References

1. Lubawski J, Saclarides TJ. Postoperative ileus: strategies for reduction. Ther Clin Risk Manag, 2008; 4 : 913 – 7.
2. Johnson MD, Walsh RM. Current therapies to shorten postoperative ileus. Cleve Clin J Med, 2009; 76 : 641 -8.
3. Steed HL, CapstickV, Flood C,Schepansky A, Schulz J, Mayes DC. A randomized controlled trial of early versus "traditional" postoperative oral intake after major abdominal gynecologic surgery. Am J Obstet Gynecol, 2002; 186(5): 861-5.
4. Charoenkwan K, Philipson G, Vutyavanich T. Early versus delayed (traditional) oral fluids and food for reducing complcations after major abdominal gynaecologic surgery. Cochrane Database Syst Rev 2007; 4 : CD004508.
5. Wolff BG, Viscusi ER, Delaney CP, Du W, Technel L. Patterns of gastrointestinal recovery after bowel resection and total abdominal hysterectomy : pooled results from the placebo arms of alvimopan phase III North American Clinical Trails. J Am Coll Surg, 2007; 205 (1) : 43 – 51.
6. Zhuang CL, Ye XZ, Zhang CJ, Dong QT, Chen BC, Yu Z. Early versus traditional postoperative oral feeding in patients undergoing elective colorectal surgery: a meta-analysis of randomized clinical trials. Dig Surg 2013; 30 : 225 – 32.
7. Ertas IE, Gaungorduk K, Ozdemir A, Solmaz U, Dogan A, Yildirim Y. Influence of gum chewing on postoperative bowel activity after complete staging surgery for gynecological malignancies: a randomized controlled trial.Gynecol Oncol 2013; 131 : 118 – 22.
8. Muller SA, Rahbari NN, Schneider F, Warschkow R, Simon T, Von Frankenberg M, et al. Randomized clinical trial on the effect of coffee on postoperative ileus following elective colectomy. Er J Surg 2012; 99 : 1530 – 8.
9. Dulskas A, Klimovskij M, Vitkauskiene M, Samalavicius NE. Effect of coffee on the length of postoperative ileus after elective laparoscopic left –

sided colectomy: a randomized, prospective single – center study. Dis Colon Rectum 2015; 58 : 1064 – 9.

10. Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Sten B, Carli F. Intravenous lidocaine versus thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using a enhanced recovery program. Reg Anesth Pain Med 2011; 36 : 241 -8.
11. Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. Postoperative ileus: recent developments in pathophysiology and management. Clin Nutr 2015; 34 : 367 – 76.
12. Narita K, Tsunoda A, Takenaka K, Watanabe M, Nakao K, Kusano M. Effect of mosapride on recovery of intestinal motility after hand – assisted laparoscopic colectomy for carcinoma. Dis Colon Rectum 2008; 51 (11): 1692 – 5.
13. Toyomasu Y, Mochiki E, Morita H, Ogawa A, Yanai M, Ohno T, et al. Mosapride citrate improves postoperative ileus of patients with colectomy. J Gastrointest Surg 2011; 15 : 1361 -7.
14. Drake TM, Ward AE. Pharmacological management to prevent ileus in major abdominal surgery: a systematic review and meta – analysis. J Gastrointest Surg 2016; 20 : 1157 – 72.
15. Tan EK, Cornish J, Darzi AW, Tekkis PP. Meta-analysis : alvimopan vs pladebo in the treatment of postoperative ileus. Aliment Pharmacol Ther 2007; 25 : 47 – 57.
16. Beck DE, Sweeney WB, McCarter MD. Prospective, randomized, controlled, proof –of – concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. Int J Colorectal Dis 2014; 29 : 1527 – 34.
17. Inui A, Yoshikawa T, Nagai R, Yoshida N, Ito T. Effects of mosapride citrate, a 5-HT4 receptor agonist, on colonic motility in conscious guinea pigs. Jpn J Pharmacol 2002; 90 (4) : 313 – 20.
18. Kadowaki M, Wang XO, Shimatani H, Yoneda S, Takaki M. 5-HT4 receptor enhances the propulsive power of the peristaltic reflex in the rat distal colon. Auton Neurosci 2002; 99 (1) : 62 – 5.
19. Kim HS, Choi EJ, Park H. The effect of mosapride citrate on proximal and distal colonic motor function in the guinea – pig in vitro. Neurogastroenterol Motil 2008; 20 (2) : 169 -76.
20. Minc Y, Yoshikawa T, Oku S, Nagai R, Yoshida N, Hosoki K. Comparison of effect of mosapride citrate and existing 5-HT4 receptor agonists on gastrointestinal motility in vivo and in vitro. J pharmacol Exp Ther 1997; 283(3): 1000 – 8.
21. Sakurai –Yamashita Y, Yamashita K, Kanematsu T, Taniyama K. Localization of the 5-HT(4) receptor in the human and the guinea pig colon. Eur J Pharmacol 1999; 383(3): 281-5.
22. Shimatani H, Kojima Y, Kadowaki M, Nakagawa T, Fujii H, Nakajima Y, et al. A 5-HT4 agonist mosapride enhances rectorectal and rectoanal reflexes in guinea pigs. Am J Physiol Gastroinest Liver Physiol 2003; 285(2) : G389 – 95.
23. Shukla D, Chakraborty S, Singh S, Mishra B. Muth dissolving tablets 1 : An overview of formulation technology. Scientia Pharmacentica 2009; 76 : 309 – 326.
24. Uitenbroke DG. SISA binomial. Southampton: D.G. Uitenbroke. Retrieved November 1, 2014, from the World wide Web: http://www.quantitativeskills.com/sisa/distributions/binomial.htm.
25. MedCalc Statistical Software version 16.4 (MedCalc Software bvba, Ostend, Belgium; from the World wide Web: https://www.medcalc.org;2016).
26. Vathe R, O'Grady G, Bissett JP, Dinning PG. Postoperative ileus: mechanisms and future directions for research. Clin Exp Pharmacol Physiol 2014; 41 : 358 – 70.
27. Endo J, Nomura M, Morishita S, Uemura N, Inoue S, Kishi S, et al. Influence of mosapride citrate on gastric motility and autonomic nervous function: evaluation by spectral analysis of heart rate and blood pressure variabilities, and by electrogastrography. J Gastroenterol 2002; 37 : 888 – 95.